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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,060	01/04/2002	Andrew Koff	14538A-005111US	5760

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,060	KOFF ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/31/2005 has been entered. Applicant amended claim 1,4-10 and the specification. Claims 1-11 are pending in the instant application. Applicant should note that the examiner of record has changed to Dr. Louis D. Lieto of ART Unit 1632.

Specification

The objection of record regarding the description of various figures in the specification is withdrawn in view of the applicant's amendments to the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *ex vivo* method for increasing the proliferation of thymocytes in a non-human animal comprising disrupting an endogenous gene

encoding $p27^{Kip1}$, wherein the $p27^{Kip1}$ gene is altered by inserting a nucleotide sequence encoding a positive selectable maker in the endogenous $p27^{Kip1}$ gene, mutation or deletion of the endogenous $p27^{Kip1}$ gene, in an isolated thymocyte, or an isolated hematopoietic progenitor cell that differentiates into a thymocyte, from a non-human animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, re-introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to the donor non-human animal thereby increasing the proliferation of thymocytes in the animal, does not reasonably provide enablement for a method for increasing the proliferation of thymocytes in a non-human animal comprising any method of altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, or any isolated multipotent cell from any animal that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to any non-human animal of any species thereby increasing the proliferation of thymocytes in the animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The amended claims encompass an *ex vivo* method for increasing the proliferation of thymocytes in any non-human animal comprising any method of altering an endogenous gene encoding $p27^{Kip1}$ in any isolated thymocyte or any isolated multipotent cell that will differentiate into a thymocyte, including ES cells, from any animal and administering the altered cells to any non-human animal of any species

The phrase embryonic stem (ES) cells has a distinct meaning in the art. Thomson et al. teaches that the defining characteristics of the ES cell is, (i) derivation from the preimplantation or periimplantation embryo, (ii) prolonged undifferentiated proliferation, and (iii) stable development potential to form derivatives of all three embryonic germ layers {Thomson et al. (1998) Science, Vol. 282, page 1145, paragraph 1}. Campbell et al. teaches that, in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species. However, as yet there are no reports of any cell lines, which contribute to the germ line in any species other than the mouse {Campbell et al. (1997) Theriogenology, Vol. 47 (1), page 65, paragraph 2}.

Further, as was stated in the previous office action of 11/7/03; in addition to the limitation of making transgenic animals, the art of culturing and maintaining ES cells in culture was also unpredictable at the time of the invention. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most strains have so far proved refractory to the derivation of cell lines..." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unpredictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by co-

culturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that such differentiation-inhibitory derived cells from the mouse do not adequately prevent differentiation of stem cells in species other than the mouse. For example, rat ES cells, capable of producing chimeras, grow best on primary rat embryonic fibroblasts as the feeder layer (see last para in col 1 on page 1558 in Mullins and Mullins, 1996) (Mullins LJ and Mullins JJ. J. Clin. Invest.97:1557-1560, 1996).

The specification does not provide an enabling disclosure on how to use any thymocyte or any isolated multipotent cell from any non-human animal that differentiates into a thymocyte in order to increase the proliferation of thymocytes in any other non-human animal. The claims encompass the administration of xenogeneic, allogeneic and autogeneic cells of neuronal origin that are oxidative stress-resistant. The specification does not teach that any thymocyte or any isolated multipotent cell, with or without a $p27^{Kip1}$ gene are sufficient to over come the immune system mediated hyperacute rejection of xenogeneic tissues due to differences in surface carbohydrate moieties among different species. The hyperacute rejection of xenotransplants is mediated by antibody response to differences in surface protein carbohydrate modifications and, not MHC expression. Gojo et al. teaches that the T cell response to porcine xenotransplants is secondary to the natural immune barrier of hyperacute rejection of porcine tissues due to the Gal α moiety {Gojo et al. (2000) Transplantation. 69:1995-1999; pgph 12}. Further, the specification does not disclose that the thymocyte or isolated multipotent cell are typed for MHC mismatches prior to administration. MHC mismatches between different tissues triggers NK; T cell and antibody mediated paths of rejection. The specification

does not disclose any working examples that describe administration of any thymocyte or any isolated multipotent cell are with a disruption in the $p27^{Kip1}$ gene are capable of preventing rejection. Thus, based on the art recognized unpredictability of isolating and culturing embryonic stem cells or other totipotent embryonic cells from mammals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonic cells from any animal species, and the lack of enablement for a method of xenogeneic or MHC mismatched allogeneic transplantation, the skilled artisan would not have had a reasonable expectation of success in isolating and using any embryonic stem cells, or embryonic germ cells according to the instant invention, an *ex vivo* method for increasing the proliferation of thymocytes in a non-human animal comprising altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, an isolated multipotent cell from a mouse that differentiates into a thymocyte, or an isolated bone marrow cell from an animal that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to the animal thereby increasing the proliferation of thymocytes in the animal, without undue and extensive experimentation.

Response to Arguments

Applicant's arguments filed 1/31/2005 have been fully considered but they are not persuasive. It is noted that applicant amended the claims so that they now only encompass a method of *ex vivo* cell therapy in non-human animals. In view of the amended claims the previous rejections pertaining to lack of enablement for making and

using any $p27^{Kip1}$ transgenic animal is withdrawn.

However, the office actions of 11/07/2003 and 7/28/2004 the examiner rejected the claims because the claims did not recite any particular threshold for targeting specificity or of clinical therapeutic efficacy for any method of altering a $p27^{Kip1}$ gene, where the intended use is *ex vivo* therapy. Further, as was stated in the previous office action of 11/7/03: Miller et al (FASEB J. 9:190-199, 1995) discussed the state of the art of targeted vectors for gene therapy and noted that there is requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells in *ex vivo* and that that these systems should be efficient and accurate. They further stressed that the range of different diseases means that no single delivery system is likely to be universally acceptable and that the stringency with which the therapeutic genes need to be accurately delivered could greatly vary, for example, a vector system used for gene delivery in cystic fibrosis tissue would not be suitable for cancer gene therapy (see first paragraph in column 1 on page 190). See also pages 4-5 of or evidence traversing this rejection. Applicant did not provide any arguments or supporting evidence traversing this rejection. Therefore it is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's amendments, see claims 4-8, filed 3/21/2005, with respect to being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been fully considered and are persuasive. The rejection of claims 4-8 has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-11 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Roberts JM et al (US Patent No 5,958,769, dated 8-28-99, filing date 1-18-1996).

It is noted that applicant's amended claims only encompass *in vitro* or *ex vivo* methods for altering an endogenous gene encoding $p27^{Kip1}$. However, the teachings of Roberts et al. also anticipates amended claims 1-11.

Roberts et al. provides guidance on an ex vivo method, wherein hematopoietic precursor cells are isolated from bone marrow (pgph 27). Further Roberts et al. teaches that endogenous gene encoding $p27^{Kip1}$ is altered by:

> a sequence comprising or encoding an oligonucleotide p27 inhibitor, e.g., triplex forming oligonucleotides, antisense oligonucleotide, ribozyme, etc., or a combination of such inhibitors targeted to different portions of the p27 DNA or corresponding RNA can be delivered in a wide variety of ways to targeted cells to facilitate progression of the cell cycle. The oligonucleotides can be administered as synthetic oligonucleotides or expressed from an expression vector. (pgph 15).

Wherein the synthesized oligonucleotides may be introduced into suitable cells by a variety of means including electroporation or microinjection (pgph 9). Roberts et al. also provides guidance on the use of a plasmid pPNT containing the neomycin resistance gene and the thymidine kinase gene. Roberts et al. teaches that after the cell population treated with $p27^{Kip1}$ inhibitor is transduced or transfected ex vivo the cells are

cultured with a selection agent such as neomycin used in the vector, and then may be returned to the host or expanded until a sufficient number of cells are available for return to the host (pgph 25). Finally, Roberts et al. teaches inhibition of $p27^{Kip1}$ produces hypercellularity of the spleen and thymus in mice (see lines 30-37 in column 19).

Response to Arguments

Applicant's arguments filed 1/31/05 have been fully considered but they are not persuasive. Applicants have asserted that the invention is not anticipated by Robert et al in view of a declaration under 37 CFR 1.131, however, no such declaration has been submitted and therefore the rejection is maintained.

No Claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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